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A cooperative trial on the primary prevention of ischaemic heart disease using clofibrate: design, methods, and progress *

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The paper describes the design of, and the procedures used in a double blind randomized trial to determine whether the incidence of ischaemic heart disease can be lowered by the reduction of high and moderately high lipid levels in healthy men aged 30–59 years. The trial started in Edinburgh in 1965 and was extended to Prague and Budapest in 1966 and 1967. It is coordinated and controlled by a committee of investigators convened by the World Health Organization. The subjects were selected on the basis of a preliminary determination of serum cholesterol level. Half of the men in the upper third of the distribution of cholesterol values have been assigned at random to a treated group and take 1.6 g of clofibrate daily; the other half make up a control group and take identical capsules containing 300–350 mg of olive oil. A second control group, chosen at random from the lowest third of the cholesterol distribution, also receives the olive oil capsules. The study is designed to have a 90 % chance of detecting, in the treated group, a reduction of one-third in the incidence of ischaemic heart disease if this should occur. The subjects are examined at the beginning of the trial, then at 6-month intervals for 2 years, and thereafter annually for at least 3 further years. The criteria of ischaemic heart disease are defined and the different control procedures are described. The required 15 000 subjects have now been admitted to the trial and their characteristics are described, but it is too early to report any results.

Ischaemic heart disease is the main health problem in middle-aged men in affluent societies and its prevention is one of the most crucial challenges to community health today. Until more is known about the pathogenic mechanisms that initiate the disease, particularly atherosclerosis, it is hoped that the correction of abnormalities associated with the disease might prevent its onset, and it is considered sound to test this approach by means of " intervention studies " (Morris & Gardner, 1969; Morris, 1970).

Hyperlipidaemia is one of the most important of these abnormalities and has been shown in a number of studies to be one of the best independent predictors of future ischaemic heart disease in otherwise healthy men (Dawber et al., 1957; Kannel et al., 1966; Morris et al., 1966; Carlson & Böttiger, 1972). Although it can be reduced by both diet and drugs, it is not known to what extent such reduction would reduce the incidence of the disease. Drug control became practical about 1962 after the initial trials of clofibrate (Thorp & Waring, 1962; Thorp, 1962; Oliver, 1962, 1967; *J. Atheroscler. Res.*, 1963), which was chosen for this trial because it reduces hypercholesterolaemia and hypertriglyceridaemia in most men by an amount that could, on the basis of published information (Truett et al., 1967), lead to a substantial reduction in the incidence of ischaemic heart disease. It removes accumulated lipids such as xanthomata and lipaemic exudates from tissues, increases the excretion of neutral sterols in the faeces, lowers serum free fatty acids, lowers plasma fibrinogen, and may have other, as yet incompletely determined, effects on the coagulation system. No toxic effects have been reported and the side effects associated with it are quite small—an important consideration not only from the ethical, but also from the design point of view, since side effects can nullify the " blindness " of a trial.

The principal objective of the trial described in

* It is hoped that further reports on the progress of the trial will be published.

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this paper is to determine whether the incidence of ischaemic heart disease can be lowered by the reduction of high and moderately high blood lipid levels in otherwise healthy men aged 30–59 years by the use of clofibrate.

After a period of initial planning, the pilot phase of the trial began in Edinburgh, in April 1965, and the trial proper in September 1965. In order to include a sufficient number of subjects the trial was extended to Prague and Budapest in 1966 and 1967, respectively. From the inception of the trial the Medical Research Council's Social Medicine Unit in London has been responsible for its design and technical conduct; it is also the data processing centre. Coordination of the trial has been undertaken since 1966 by the World Health Organization (Oliver, 1968, 1970).

DESIGN OF THE TRIAL

The population participating is divided into three equal groups on the basis of the distribution curve of serum cholesterol levels in blood samples obtained at preliminary screening visits. The third with the highest serum cholesterol levels are all eligible for inclusion in the trial as are a randomly chosen half of the third with the lowest cholesterol levels. Those in the middle third and the remaining half of the lowest third are excluded. Thus only half of those screened are eligible for inclusion. The men in the third with the highest levels are further divided at random into two equal-sized groups, one of which, the treated group, is given clofibrate and the other, the control group, is given identical capsules containing 300–350 mg of olive oil. The group with the lowest serum cholesterol levels also receives the control regimen. There are, therefore, three groups: (1) men with the highest serum cholesterol levels receiving clofibrate, (2) men with the highest serum cholesterol levels receiving the control regimen, and (3) men with the lowest serum cholesterol levels receiving the control regimen (this design is illustrated in Fig. 1 of Oliver, 1970).

The essential part of the trial is the comparison of groups (1) and (2), men with high and moderately high serum cholesterol levels. To test the treatment in men whose cholesterol was not raised would involve ethical problems and would, in any case, have limited public health application. The purpose of including a group of men with low serum cholesterol levels is two-fold. It allows the examining physicians to reassure the volunteers that they have not necessarily been selected because they have elevated serum cholesterol levels: this assurance can be given since the physicians concerned do not know a subject's cholesterol level (see below), and goes far towards preventing any possible " cholesterol neurosis ". The second objective is to provide a control or contrast group of men with naturally occurring low serum cholesterol levels in whom the incidence of myocardial infarction will be expected to be low and can be compared with that of the treated group.

The trial is double-blind—neither the examining physicians nor the subjects know which preparation is being given, nor do they know the individual serum cholesterol levels. In a sense it is, in fact, triple-blind, since so far none of the results have been communicated to any of the workers in the trial (see below under " Statistical Assessment "). As is usual in such clinical trials, provision is made for breaking the code in a medical emergency.

The three centres (Edinburgh, Prague, and Budapest) each contribute approximately equal numbers of subjects, and the essential elements of the design are the same in each centre. In particular, randomization is carried out separately for each centre so that the design is balanced in respect of differences between centres. Differences in the type of subjects recruited in the three centres are detailed below, as are important differences in procedure.

Numbers of subjects

In calculating the required number of subjects for the trial the following considerations were taken into account.

Expected reduction in incidence due to treatment. The study is designed to detect, with a high degree of probability, a reduction of one-third in the incidence of ischaemic heart disease. This figure was chosen in the light of published evidence (Truett et al., 1967) of the relationship between blood cholesterol and the incidence of this condition and after consideration of the likely reduction in cholesterol levels from taking clofibrate.

Untreated incidence. The annual incidence of ischaemic heart disease in untreated men aged 30–59 years in the upper third of the cholesterol distribution has been postulated to be 1% per annum.

The period of the study was taken as at least 5 years.

Significance level. The 1% level of significance will be used to asses differences, i.e., α (two-sided)$=0.01$.

Power. The power of the study to detect a differ-

ence in incidence of 1/3 at the 1% level of significance will be approximately 90%, i.e., β (one-sided)=0.10.

Drop-out. It has been assumed that 30% of subjects will not continue to the end of the trial.

With these assumptions it was calculated that 15 000 subjects would be needed to start the trial, 5 000 in each group and 5 000 in each centre. Since only half the subjects screened were eligible and, of this half, a proportion did not agree to participate, and some men were excluded for various medical reasons, more than 50 000 had, in fact, to be screened (Table 1).

DRUG SCHEDULE

The clofibrate for this trial is prepared in an opaque, white, gelatine capsule containing 400 mg. Capsules identical in size, shape, and appearance containing olive oil are used for the control groups.[1] The subjects take 2 capsules in the morning and 2 at night so that the men on clofibrate receive 1.6 g daily. The capsules are dispensed in small round tins with a screw top, each containing 1 week's supply; 30 of these tins are packed together in a light cardboard case for distribution to the men, i.e., a 6-month supply at a time. The outside of each tin is labelled " Heart Disease Prevention Trial. Take two capsules twice daily ". There is no means of distinguishing between the active and the control capsules on the tin or on the pack. The pack has the man's name and trial number written on the outside.

RECRUITMENT, INITIAL EXAMINATIONS, AND FOLLOW-UP

Main sequence of events

Screening started in Edinburgh early in 1964 and the first subjects were admitted to the trial in April 1965. It soon became apparent that the numbers in Edinburgh alone would not be sufficient and the other two centres joined the trial in 1966. Screening in Prague began in December 1966, and in Budapest in March 1967. Both of these centres started admitting men to the trial late in 1967.

The subjects

In Edinburgh, the great majority of the men (69%) are volunteer blood donors cooperating with the South East Scotland Regional Blood Transfusion Service. Some 39% of the donors attend the Edinburgh clinics, but the remainder are drawn from other parts of south-eastern Scotland. The remaining 31% of the Edinburgh men were recruited in various ways—by asking the blood donors to approach their friends, from certain general practices in Edinburgh, by press and television advertising, and from commercial undertakings. A total of 4 980 men have been admitted to the trial in the Edinburgh centre.

In Budapest, men were first recruited from lists of blood donors (31%) and later from the tuberculosis registers in certain city districts (69%). The tuberculosis registers are in fact complete population lists prepared for mass-screening and contain information about age. They thus form an excellent basis for recruitment. A total of 5 359 men have been admitted to the trial in Budapest.

In Prague, the lists of addresses in the electoral rolls for three of the city districts are used. Since age is recorded in these rolls it is possible to choose selected age groups. A total of 5 437 men have been admitted to the trial, in Prague. In both Edinburgh and Budapest the switch from a blood donor population to other systems of recruitment became necessary because initial estimates of the numbers available proved to be overoptimistic.

The grand total of men admitted to the trial is 15 776.

Screening

As mentioned above, the men are selected for the trial on the basis of serum cholesterol values obtained at preliminary screening visits. The arrangements for these varied in detail in the three centres for practical reasons, but there is one substantive difference. It became clear in Edinburgh that cholesterol levels in the same individual vary considerably, with the result that the separation of the men with high and low cholesterol levels into groups was not as effective as it should have been. In fact, a few men classified as high on the basis of a screening value showed lower cholesterol levels at the next examination (the first visit of the trial proper, at which treatment was started) than men whose screening value had placed them in the lowest third of the distribution. Average cholesterol levels of men classified as high and low at screening were still clearly different at the first trial visit, but the difference was not so great as it was between the mean values at the screening visit. This narrowing of the difference between group-means at the first trial visit

[1] Both sets of capsules are prepared and distributed to all centres by Imperial Chemical Industries, Pharmaceuticals Division, Macclesfield, England, the manufacturer of clofibrate.

(" regression to the mean ") was to be expected on theoretical grounds, and the amount of regression can now be closely predicted given the relative sizes of the " between individual " and " within individual " variances in cholesterol levels.[1]

The remedy is to base the screening on more than one value, which has accordingly been done in Prague and Budapest (where two initial values are used), and this has in fact resulted in a reduction of the regression effect. Unfortunately, by the time the phenomenon had been appreciated, the trial was too far advanced in Edinburgh to make the corresponding change there.

The three centres differ in the amount of ancillary information recorded at the screening visit. In Prague and Budapest this is used to exclude certain subjects on medical grounds.

Admission to the trial

Although there are local differences in procedure, all subjects pass through the following three essential steps before admission: (1) selection on the basis of a screening cholesterol value, (2) medical examination, and (3) explanation of the purpose of the trial.

Detailed criteria for rejection on medical grounds are listed in Annex 1. Essentially they consist of evidence of previous myocardial infarction or other heart disease, hypertension, or diabetes, or of co-existing disease with a severe prognosis, such as cancer or stroke.

If a man passes the first two stages and agrees to participate, he is then admitted to the trial. Those in the high cholesterol groups are allocated to the clofibrate or control regimen at random and independently of the system of selection and admission.

A record, essentially the same in each centre, is completed at the first trial visit for every subject. The information recorded includes the man's socioeconomic group, smoking habits, responses to the standard questionnaires [2] on ischaemic chest pain and intermittent claudication (Rose & Blackburn, 1968), and family history. The results of the physical examination are, of course, also recorded, together with his height, weight, skinfold measurements, blood pressure, presence of arcus senilis or xanthomata, auscultatory findings over the heart, and a 12-lead resting electrocardiogram. Blood is taken for lipid analysis.

The man is then given a 6-month supply of capsules.

Follow-up procedure

Each man is seen at 6-month intervals for the first 2 years and annually thereafter. At each follow-up visit a record is completed, which is similar to that made at the first visit, but which contains answers to questions about changes in habits (particularly smoking) and about regularity in taking the drug, and a record of any symptoms or side effects that the subject attributes to the capsules. Men who give a positive answer to the questionnaire on chest pain related to effort, and whose resting ECG is negative, are given a further ECG examination after exercise on a bicycle ergometer under conditions for stress-testing closely similar to those recommended for patients after myocardial infarction. (WHO Meeting on Exercise Tests in Relation to Cardiovascular Function, 1968). Blood is taken at each visit, mainly for lipid analysis but also for testing adherence to the drug regimen (see below), and a sufficient supply of capsules is given to last until the next visit.

When the visits become annual, the participants are sent a postal questionnaire at the 6-month stage between visits or are reached in other ways. The questionnaire inquires about symptoms that may indicate heart trouble and about any difficulties with the capsules. If there is any indication of anything unusual, subjects are recalled to the clinic at this stage for interview.

If at any stage a man fails to keep an appointment he is offered two more appointments before he is considered to have lapsed or defaulted. Every endeavour is made to find out whether the man is still alive and well and why he has not returned. All men who have left the trial because they have moved away from the district or simply decided not to continue in it are sent a questionnaire or reached in some way after 6 months to establish their current state of health in case the reason for leaving was in some way connected with unrecognized incipient heart disease. In the Edinburgh centre, the names of those who have left the trial are given to the office of the Registrar-General for Scotland, which informs us if any of them should leave the district or die. In this event a copy of the death certificate is obtained. Every subject in the centre will eventually be covered by this system.

In Edinburgh the first men to enter the trial have completed 5 years' participation. These men have been asked to continue in the trial and, to date, 95% have agreed to do so for 2 further years. Table 1

[1] Gardner, M. J. (1971) *Some problems in prediction and measurement with application in medical studies* (thesis, University of London).

[2] London School of Hygiene and Tropical Medicine.

Table 1. Numbers of subjects at different stages in trial, March 1972

Stage	Edinburgh	Budapest	Prague	All centres
screened	18 748	15 540	18 231	52 519
rejected for medical reasons	126	149	429	704
admitted to trial [a] (i.e., 1st visit)	4 980	5 359	5 437	15 776
2nd visit (6 months)	4 473	4 964	5 052	14 489
3rd visit (1 year)	4 144	3 777	4 814	12 735
4th visit (1½ years)	3 668	3 067	4 611	11 346
5th visit (2 years)	3 348	2 180	3 688	9 216
6th visit (3 years)	2 395	880	699	3 974
7th visit (4 years)	1 587	153	93	1 833
8th visit (5 years)	1 019	—	—	1 019
9th visit (6 years)	293	—	—	293

[a] Half those otherwise eligible were excluded because of the cholesterol levels found at the preliminary screening.

shows the numbers of participants at different stages in the trial in the three centres at the end of March 1972.

Advice on other risk factors

No advice is given on diet, weight reduction, smoking, or exercise unless requested by the subject, in which case the physician gives what he considers to be the appropriate clinical advice for the individual.

Test of adherence to the clofibrate regimen

At each visit blood samples are taken from all men receiving the active drug and are tested for the presence of clofibrate;[1] the same is also done for a random 10% of the controls in order to maintain an element of " blindness " in the laboratories. When the blood from a subject who should be taking clofibrate is found on two successive visits to be negative, arrangements are made to check that he has been receiving the right treatment, that he has not himself been reporting failure to take the capsules, and that he has not been taking any drugs, such as salicylates, that could interfere with the test. If none of these considerations apply, he is interviewed by a physician not actively involved in the trial clinics to find out if there is any explanation.

[1] The substance measured is in fact 2-(*p*-chlorophenoxy)-2-methylpropionic acid.

Removal from the trial for medical reasons

A man may be removed from the trial after entry for the reasons indicated in Annex 2. Essentially these consist of the occurrence of myocardial infarction, hypertension, diabetes, or heart disease as previously defined; together with contraindications for taking the capsules such as serious apparent side effects. Angina related to effort is not a reason for removal.

Lapses or " drop-outs "

Apart from those men who are removed, or who remove themselves, from the trial for medical reasons, there is, of course, a proportion who are not able or do not wish to continue in the trial for other reasons. These have been classified as " moved away " when this is stated, or " opted-out " when they have stated that they do not wish to continue. If they simply fail to attend they are so classified. It is, of course, of interest to examine the distribution of the various categories of lapses and exclusions by regimen because the reason given may not be the main reason and may well be related to treatment. The position in March 1972 is shown in Table 2. There do not appear to be any important differences between the regimens. The numbers excluded for medical reasons, in particular, are very similar. The proportions of subjects who have lapsed or been excluded under the various headings differ considerably in the three centres but this is likely to be related to the types of subject included in the centres and to differences in screening practices in the pretrial period. All men who lapse or are excluded are considered to be in the trial up to their last visit, but the results of the 6-month follow-up after leaving the trial are examined in relation to regimen.

Table 2. Lapses and exclusions, March 1972

Reason	Regimen			Total
	Clofibrate: high cholesterol	Control: high cholesterol	Control: low cholesterol	
medical reasons	177	182	160	519
moved away	68	87	108	263
opted out	342	321	338	1 001
failed to attend	225	216	219	660
total	812	806	825	2 443

It is interesting to compare the proportions of subjects who have dropped out at various stages (i.e., who have been excluded or who have lapsed) in relation to the total number who could have reached that stage if there had been no drop-out with the 30% allowance for drop-out in 5 years made in calculating the required numbers for the trial. The allowance of 30% was for 10% in the first year and 5% in each of the 4 subsequent years. The cumulative percentage drop-out [1] at each centre so far is shown below.

Drop-out after	*Edinburgh*	*Budapest*	*Prague*
1 year	11	10	7
2 years	16	19	13
3 years	19	24	14
4 years	22	26	—
5 years	23	—	—

So far, this is well within the original estimates and the great majority of the men who remain in the trial appear to be well satisfied.

Endpoints for assessing the result of the trial

The result of the trial will be assessed by the difference in incidence (i.e., new events arising during the course of the trial) of the following endpoints in the two high cholesterol groups: (1) myocardial infarction as defined below, (*a*) and (*b*), or (2) death from myocardial infarction, or (3) sudden, unexplained death when it is not possible with certainty to exclude acute myocardial infarction (ischaemia) and this is postulated to be the cause, or (4) myocardial ischaemia as defined below, (*c*), (*d*), and (*e*).

Definitions of endpoints

Myocardial infarction is said to be present when:

(*a*) the Minnesota coding of the resting ECG is 1-1, 1-2, or 9-6 (new category—see later under ECGs); or

(*b*) the Minnesota coding of the resting ECG is 1-3, with " serum enzyme changes " *or* with " symptoms ".

Myocardial ischaemia is said to be present when:

(*c*) there is complaint of prolonged chest pain at rest and the Minnesota coding of the resting ECG is 4-1, 5-1, or 7-1; or

(*d*) the response to the effort chest pain questionnaire is positive and the Minnesota coding of the resting ECG at the same or a previous visit is 4-1, 4-2, 5-1, 5-2, 6-1, 6-2, 7-1, or 8-3; or

(*e*) the response to the effort chest pain questionnaire is positive, the resting ECG is negative, and the Minnesota coding of the required postexercise ECG is 11-1, 11-2, 12-1, 12-2, or 14-1.

" Serum enzyme changes " are interpreted in each centre according to locally accepted ranges of normal/equivocal/abnormal. " Symptoms " are complaints of chest pain of half an hour or more, acute breathlessness, or syncope.

All deaths are recorded with as much detail as possible. A careful check is made to define the causes of death and to distinguish death resulting from myocardial infarction and other cardiovascular causes from that resulting from noncardiovascular causes. Autopsy data are obtained wherever possible. In addition, death certificates and hospital records are used and every attempt is made to establish the duration of the terminal events when death is sudden and unexpected. " Sudden death " is defined as death occurring within 1 hour of the onset of symptoms or last being seen alive. A sudden death is assumed to be due to acute myocardial infarction (ischaemia) when, after examination of all available evidence, it is not possible to exclude this as a cause. It will of course be possible later to examine separately the various subcategories defined above for any relationship with treatment.

It will also be possible to examine other relevant phenomena, both separately and together with myocardial infarction and ischaemia. For this purpose the following categories have been defined: (1) a positive answer to the ischaemic pain questionnaire without relevant ECG findings; (2) a positive answer to the intermittent claudication questionnaire; (3) nonfatal cerebrovascular disease—a single episode of motor paralysis, sensory or speech dysfunction, diplopia, or visual disturbance, lasting for 1 hour or more; or repeated episodes of a similar nature lasting 5 minutes or more.

Notification procedure

All events, whether related to myocardial infarction or to other manifestations of ischaemic heart disease, all deaths, and all exclusions and lapses from the trial are notified to the London centre as they occur.

Review panel

A panel reviews all events that the participating physicians in the three centres consider might be due to myocardial infarction, as defined. Relevant documents, including serial ECGs and laboratory findings,

[1] As a proportion of all those who could have reached the stage indicated.

are sent to Geneva for consideration by the panel, which consists of two regular members not concerned with the day-to-day running of the trial who may coopt another specialist in cardiology. The main purpose of the review panel is to draw the attention of centres to any differences in interpretation of the criteria. A consolidated report is presented at the annual meeting of those concerned with the trial.

STANDARDIZATION OF PROCEDURES

Serum cholesterol

Each centre is responsible for its own serum cholesterol estimations and, in fact, three different methods are used (see below). Careful control and standardization is therefore necessary and is organized at three levels: (1) intralaboratory (i.e., within each centre); (2) interlaboratory (i.e., by exchange of pooled sera, etc.); and (3) by reference to WHO international reference centres.

(1) The quality control in each centre will naturally vary with the method, but in each run all the laboratories estimate standard solutions, pooled serum, and carry-over samples from the previous batch. A variation of more than 5% indicates the necessity for a re-run of the estimation. There are also controls on the frequency of preparation and dilution of stock solutions and a watch is kept on the possibility of a " drift " in standards. A copy of the detailed methods used is available in each laboratory for the technicians to consult. An Autoanalyzer is used in Edinburgh, but not in Prague or Budapest. Duplicate samples are run in all centres.

(2) From time to time—at approximately 6-month intervals—200 vials of pooled serum are circulated to each centre, 100 of high and 100 of low concentration, for use in the daily control system. The results of the estimations in each laboratory on these pooled sera are examined regularly to control interlaboratory variation.

(3) Each laboratory has also participated in the Cholesterol Standardization Programme organized by the WHO International Reference Centre in Atlanta, Ga., USA (Beaumont et al., 1970). Dr G. Cooper of the Reference Centre acted as an adviser to the trial. [1]

The methods used in the different centres are as follows:

(*a*) In Edinburgh, serum cholesterol is estimated by means of an Autoanalyzer by a method using sulfuric acid and iron(III) chloride described by Block et al. (1966) and based on the method of Levine & Zak (1964). Up to January 1968, the serum cholesterol was estimated by the manual method described by Jurand & Albert-Recht (1964).

(*b*) In Budapest, the Abell–Kendall method with the modification of Anderson was used until January 1969: 1 644 men were admitted to the trial on the basis of this method and are included in Table 6 under Budapest (A). Because of technical problems and the increasing load on the laboratory staff the simpler Watson method has now been adopted: the 3 715 men admitted on the basis of this method are included in Table 6 under Budapest (W).

(*c*) In Prague, cholesterol estimation is carried out by the direct method of Crockett et al. (1963) as modified by Grafnetter et al. (1967).

It is clear from Table 6 that serum cholesterol levels, as determined, differ considerably in the three centres, notably between Edinburgh and Prague. It has, however, been established by the Reference Centre in Atlanta that these differences are entirely due to the methods used. Comparison of serum pools, and of sets of sera circulated for " blind " comparison, also shows little systematic difference between centres.

From the results shown in Table 6 it is also clear that despite the division into the high and low thirds of the cholesterol distribution on the results of the analyses carried out at the screening visits, there was still some overlap in the serum cholesterol values at the first trial visit. This is particularly noticeable in the data from Edinburgh and Budapest and is partly a result of seasonal and other variation in the " cut-off " points separating the thirds of the distribution within a centre. It is also a result of the " regression to the mean " effect mentioned above and, of course, of the considerable individual variability in an individual's serum cholesterol with time.

Serum triglycerides (non-fasting)

These are estimated in Edinburgh men only by an Autoanalyzer method in 10% of the subjects.

ECGs

The ECGs are classified by the revised Minnesota Code (Blackburn, 1960; Rose & Blackburn, 1968). Two observers at each centre read each ECG independently and " blind " in the sense that they do not know anything about the subject or about any of his

[1] Recently the Prague laboratory, under Dr D. Grafnetter, has been constituted a WHO lipid reference centre and has taken over this work.

previous ECGs. One of these readers, designated the " key reader ", reads every ECG; the identity of the second reader will vary from time to time. At least one of the two readers must be medically qualified. If there is any disagreement in the coding the two readers consult and agree on a coding. If this should prove impossible, or if the difference in coding involves a question of rejection or removal from the trial, a third reader from the local team, who has no knowledge of the nature of the disagreement, is consulted.

In order to maintain comparability in coding procedures between centres, sets of ECG recordings from each centre are circulated to the other centres for coding, and the results are assessed and compared and discussed at the annual meetings of those concerned with the trial.

One modification of the Minnesota Code is used in this trial. A category 9-6 has been introduced—ST junction (J) and segment elevation (precisely defined)—and this is regarded as highly suggestive of recent intramural anterior myocardial infarction.

Skinfold thickness

To standardize this highly variable measurement for observer variability comparisons are carried out on the same subject from time to time both within centres and when the examining physicians meet at the annual meetings. Triceps and subscapular skinfolds are measured.

DATA PROCESSING

The data processing is carried out in London using the University of London's computer. Standard information on each man, recorded at each visit, is sent to London to be punched and recorded on tape. Notifications of the ischaemic events defined in an earlier section and of lapses and exclusions are also assembled in London and a continuing analysis is made of these notifications in relation to regimen.

Standard tables are produced and circulated every 6 months to all centres. Essentially these 6-monthly tables consist of: (1) descriptions of the subjects in each centre at entry to the trial in order to check the effectiveness of randomization and to provide a description of the trial population in each centre, (2) tables, by centre, of change in key variables such as cholesterol, weight, and blood pressure, by regimen and by length of time in the trial, and (3) tables of distribution of change so that, for instance, the number of men whose cholesterol does not respond to treatment or who gain weight excessively can be continuously watched.

Table 3. Percentage distribution of entrants to trial by age group

Age group (years)	Regimen			Total
	Clofibrate: high cholesterol	Control: high cholesterol	Control: low cholesterol	
		Edinburgh		
30–39	31	33	45	36
40–49	45	44	39	43
50–59	24	23	16	21
total no.	1 651	1 671	1 658	4 980
		Budapest		
30–39	20	21	35	25
40–49	45	44	38	42
50–59	35	35	27	33
total no.	1 805	1 757	1 797	5 359
		Prague		
30–39	0	0	0	0
40–49	76	75	75	75
50–59	24	25	25	25
total no.	1 886	1 882	1 669	5 437

Tables 3-7 give the results mentioned under (1) above for age, height, weight, blood pressure, serum cholesterol, and smoking habits. Since recruitment is now complete these data describe the characteristics of all the subjects admitted to the trial in the different centres and also show that, in this respect at least, the randomization has been effective since no important difference between the two high cholesterol groups is apparent in any of the characteristics in any centre.

COORDINATION AND CONTROL

The control of the trial is exercised through an annual meeting of all the investigators.[1] All the main decisions are made at these meetings (and occasionally at special meetings of the same group convened for a particular purpose). The meetings are supported by the World Health Organization, which is also responsible for issuing the subsequent reports. WHO also supports visits [2] by statisticians to the trial, and

[1] These meetings are held at each centre in turn.
[2] These are made roughly biannually.

Table 4. Percentage distribution of entrants to trial by height and weight

Characteristic	Regimen: Clofibrate: high cholesterol	Control: high cholesterol	Control: low cholesterol	Total
Height (cm)		Edinburgh		
<170	24	23	19	22
170–179	55	55	55	55
⩾180	21	22	26	23
		Budapest		
<170	48	44	40	44
170–179	44	47	50	47
⩾180	8	9	10	9
		Prague		
<170	24	26	22	24
170–179	58	57	58	58
⩾180	18	17	20	18
Weight (kg)		Edinburgh		
<70	22	21	31	25
70–89	66	66	61	64
⩾90	12	13	8	11
		Budapest		
<70	19	18	29	22
70–89	65	65	59	63
⩾90	16	17	12	15
		Prague		
<70	13	12	14	13
70–89	65	65	66	65
⩾90	22	23	20	22

by others as required, to the different centres to ensure as far as possible that the detailed procedures are uniform and to enable points of difficulty to be discussed on the spot. The London centre also acts as a clearing house for the solution of day-to-day problems arising in the trial, particularly those involving the recording system.

Table 5. Percentage distribution of entrants to trial by systolic and diastolic blood pressure

Characteristic	Regimen: Clofibrate: high cholesterol	Control: high cholesterol	Control: low cholesterol	Total
Systolic blood pressure (mmHg)		Edinburgh		
<120	12	15	15	14
120–139	46	44	51	47
140–159	30	30	26	29
⩾160	12	11	8	10
		Budapest		
<120	17	17	27	20
120–139	45	45	47	46
140–159	27	28	20	25
⩾160	11	10	6	9
		Prague		
<120	17	17	21	18
120–139	49	48	48	49
140–159	25	26	22	24
⩾160	9	9	9	9
Diastolic blood pressure (mmHg)		Edinburgh		
<80	21	23	27	24
80–89	40	37	43	40
90–99	27	27	23	25
100–109	10	10	6	9
⩾110	2	3	1	2
		Budapest		
<80	17	17	27	21
80–89	41	40	43	41
90–99	26	27	22	25
100–109	14	14	7	12
⩾110	2	2	1	1
		Prague		
<80	15	15	18	16
80–89	39	39	39	39
90–99	32	33	32	32
100–109	10	10	8	10
⩾110	4	3	3	3

Table 6. Percentage distribution of entrants to the trial by cholesterol level

Cholesterol (g/l)	Regimen: Clofibrate: high cholesterol	Regimen: Control: high cholesterol	Regimen: Control: low cholesterol	Total
		Edinburgh [a]		
<2.00	11	11	68	30
2.00–2.29	26	26	23	25
2.30–2.59	34	32	6	24
2.60–2.79	15	16	2	11
⩾2.80	14	15	1	10
		Budapest (A) [a]		
<2.00	7	5	81	31
2.00–2.29	26	28	14	22
2.30–2.59	37	30	3	24
2.60–2.79	14	17	1	11
⩾2.80	16	20	1	12
		Budapest (W) [a]		
<2.00	6	7	62	25
2.00–2.29	19	19	24	21
2.30–2.59	30	32	10	24
2.60–2.79	19	17	3	13
⩾2.80	26	25	1	17
		Prague [a]		
<2.00	0	0	34	10
2.00–2.29	0	0	55	17
2.30–2.59	20	23	11	19
2.60–2.79	28	30	0	20
⩾2.80	52	47	0	34

[a] Details of the analytical techniques used are described in the text.

Table 7. Percentage distribution of entrants to trial by smoking habits

Smoking category	Regimen: Clofibrate high cholesterol	Regimen: Control high cholesterol	Regimen: Control low cholesterol	Total
		Edinburgh		
never smoked	24	24	28	25
ex-smokers	22	22	18	21
present smokers:				
all forms	54	54	54	54
cigarette smokers [a]	45	46	45	45
<5 per day [b]	2.2	2.2	3.2	2.5
⩾20 per day [b]	23	22	20	22
		Budapest		
Never smoked	27	26	32	28
ex-smokers	20	21	17	19
Present smokers:				
all forms	54	54	51	53
cigarette smokers [a]	52	53	51	52
< 5 per day [b]	1.6	1.9	1.8	1.8
⩾20 per day [b]	34	35	33	34
		Prague		
never smoked	25	26	38	29
ex-smokers	13	13	16	14
present smokers:				
all forms	61	62	46	57
cigarette smokers [a]	60	61	45	56
<5 per day [b]	1.8	2.3	2.3	2.1
⩾20 per day [b]	40	39	27	36

[a] Those smoking cigarettes only and those smoking cigarettes and other forms of tobacco.
[b] Manufactured cigarettes.

STATISTICAL ASSESSMENT

As indicated earlier, the trial has been designed to have a good chance of showing a statistically significant difference at the 1% level between the incidence of ischaemic heart disease in the two high cholesterol groups. The main criterion of success or failure will be the incidence of myocardial infarction and ischaemia as defined earlier. The incidence of side effects is also being carefully monitored throughout the trial.

The policy has been adopted (as mentioned earlier) of not revealing the results of the trial (i.e., the relationship between the endpoints and the regimens) to the workers involved. The statisticians alone have access to the necessary data. The basic reasons for this are that early results, short of statistical significance, can be highly misleading. They may prejudice the outcome of the trial by influencing the attitude of the staff (in terms of morale, assessment of endpoints, or detailed discussion about admitting patients or ex-

cluding them for medical reasons), or the enthusiasm of supporting bodies. They may also affect medical opinion generally and hence treatment and research, before there is valid evidence. For this reason no results can be given in this report about the incidence of ischaemic heart disease in relation to regimen.

It has been agreed in principle, however, that the main results should be divulged: (1) if there is a significant result on a sequential basis against the treatment in terms of the main endpoints of the trial, (2) if there is a significant result (on a similar basis) against the treatment in terms of an important side effect where useful discussion would be inhibited by lack of knowledge of the main result, or (3) if it becomes clear that the result of treatment cannot be significantly in favour of the treatment.

The 5% significance level and a power of 90% are used in these tests, with an early warning stage at the 10% significance level to be used at the discretion of the London group.

A favourable result will not be divulged until the full planned number of events envisaged in the design of the trial has been reached unless, in the opinion of the London group, it seems important to divulge it.

DISCUSSION

The information from this trial should be useful whether the outcome is positive or negative. As has been indicated, the numbers are large enough for it to have a good chance of producing a definite result, one way or the other. If there is a positive result and the effect is mediated through reduction in serum cholesterol levels it will remain to determine which lipids and which fractions are the important ones. Analysis of the results from the trial should provide part of the answer and, of course, it will not follow that lowering of lipids by other methods will be effective. Whether or not the effect is related to lipid reduction it will be important to discover what other mechanisms are at work. In any case, if the administration of clofibrate lowers the incidence of myocardial infarction it will be a significant advance in preventive medicine even if the mechanism is not clear.

If the result is negative, and there is no important difference between the treated and the control subjects in the incidence of myocardial infarction, this will also be theoretically important since one of the main outstanding problems in this field is whether raised serum lipid levels, and particularly raised serum cholesterol levels, are causative factors in this disease or merely indicators of some other abnormality more directly involved. While a negative result would show that the lowering of the serum cholesterol level is not in itself an effective preventive measure it would not necessarily follow that other methods of lowering lipid levels would be ineffective. In particular, dietary regimes might be effective.

Although hyperlipidaemia is amenable to control in several ways, by diet or by drugs, it is easier to conduct a scientifically sound clinical trial using a double-blind and randomized design with a drug than with a diet because " blindness " is possible with a drug, but very difficult with a diet; surveillance is also much easier with a drug since its absorption can be assessed. Although in many ways it would be preferable to use a suitable diet to lower lipid levels, the procedure is more complicated, involving a much greater change in habits; drugs are therefore more likely to be acceptable to the necessary high proportion of men in normal, working populations and over the long periods of time required for trials of this sort.

In the design of the present study an important problem was the choice of the age of the subjects. To have chosen too old an age group might have meant that the drug was being tested on men in whom it had no chance of success, since atherosclerosis is established in the coronary arteries of most middle-aged men. To have chosen a young group, say men in their twenties, would have involved working with a population numbering several hundred thousand to obtain the number of events necessary for a significant result in a reasonable time. This would have been completely impracticable and, moreover, might not have reflected the situation in middle age when ischaemic heart disease is most important.

Another point in designing trials of this kind is the choice of a single risk factor for study instead of attempting to test a number of factors at the same time, which, of course, would have several theoretical advantages. Again, the main considerations were practical. A multifactor trial is much more difficult to undertake than a single factor trial. The present trial is, in fact, testing an important hypothesis in the etiology of ischaemic heart disease, possibly the most important outstanding one in terms of the natural history of the disease, and, in the process, is accumulating a fund of recorded practical experience in the management of international trials. Such trials of new treatments are likely to be increasingly common, and their promotion and coordination is the kind of work for which WHO was created.

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RÉSUMÉ

ESSAI COLLECTIF DE PRÉVENTION PRIMAIRE DE LA CARDIOPATHIE ISCHÉMIQUE PAR LE CLOFIBRATE: CONCEPTION, MÉTHODES ET DÉROULEMENT

Le présent article décrit la conception, les méthodes et les techniques mises en pratique lors d'un essai collectif à double insu visant à établir s'il est possible de réduire l'incidence des cardiopathies ischémiques en abaissant les concentrations élevées ou relativement élevées des lipides sériques chez des hommes bien portants âgés de 30 à 59 ans. Les opérations ont débuté en 1965 à Edimbourg puis se sont étendues à Prague et à Budapest en 1966 et 1967. Leur surveillance et leur coordination sont assurées par un comité formé de l'ensemble des investigateurs, patronné par l'OMS, et qui se réunit à intervalles réguliers.

Dans les trois centres précités, on a choisi au total 15 000 volontaires chez lesquels on a déterminé le taux de cholestérol sérique. Cet examen a permis de constituer trois groupes: *a*) un groupe de sujets présentant des taux élevés de cholestérol, auxquels on administre, en capsules, une dose quotidienne de 1,6 g de clofibrate; *b*) un groupe de sujets présentant aussi des taux élevés de cholestérol, qui reçoivent des capsules d'aspect identique renfermant 300-350 mg d'huile d'olive (1er groupe témoin); *c*) un groupe de sujets présentant de faibles taux de cholestérol, qui reçoivent également des capsules d'huile d'olive (2e groupe témoin). L'étude est conçue de façon à déceler, avec une probabilité de 90%, une réduction d'un tiers de l'incidence des cardiopathies ischémiques, si une telle réduction intervient. Tous les participants sont examinés à intervalle de 6 mois pendant les deux premières années, puis annuellement par la suite. Les données recueillies sont envoyées à Londres pour traitement par ordinateur et analyse. Des examens de sang sont pratiqués afin de s'assurer que le clofibrate est pris régulièrement.

L'incidence des cardiopathies ischémiques sera évaluée d'après le nombre de cas d'infarctus du myocarde, d'ischémie du myocarde et de morts subites qui seront enregistrés pendant la durée de l'étude. Tous les événements pouvant être rattachés à l'existence d'une cardiopathie ischémique font l'objet d'un examen par un groupe indépendant de cardiologues. L'essai est actuellement en cours, et le nombre requis de sujets y participe, mais il est encore trop tôt pour en évaluer les résultats.

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Annex 1

CRITERIA FOR REJECTION ON MEDICAL GROUNDS

(1) History of treated myocardial infarction with ECG signs (see 2*a* and *b* below) and/or enzyme changes (using local methods and standards). Previous ECG and hospital records must be examined. An unsubstantiated history of myocardial infarction is not a cause for rejection.

(2) ECG evidence of heart disease (Minnesota Code system):

- (*a*) ECG evidence of myocardial infarction or widespread myocardial ischaemia: i.e., category 1-1, 1-2, 4-1, 5-1, 6-1, or 9-6 (as defined);
- (*b*) complete left bundle branch block: 7-1;
- (*c*) " lone " atrial fibrillation or flutter; or
- (*d*) multiple (more than 4 in 12 complexes) or bifocal ventricular extrasystoles.

(3) Systemic hypertension:

- (*a*) a diastolic BP of 120 or greater on any one occasion; ;
- (*b*) a diastolic BP of 110–119 on any two occasions;
- (*c*) a diastolic BP of 110–119 on any one occasion if accompanied by ECG signs of left ventricular hypertrophy, or strain, i.e., 3-1, or 3-3 + 5-2 or + 5-3; or
- (*d*) if the diastolic BP is within the accepted limits but only on account of treatment with antihypertensive drugs and the ECG shows signs of left ventricular hypertrophy or strain, i.e., 3-1, or 3-3 + 5-1 or + 5-2 or + 5-3.

(4) Clinical evidence of rheumatic heart disease.

(5) Congenital heart disease.

(6) Pulmonary heart disease as defined by the World Health Organization (1961). Chronic bronchitis, emphysema, or kyphoscoliosis when associated with ECG signs of right ventricular hypertrophy or strain, i.e., 2-2, 3-2, 7-2, and 7-3.

(7) Other heart disease associated with cardiomegaly or heart failure.

(8) Diabetes mellitus requiring drug treatment.

(9) Coexisting disease with an unfavourable prognosis reducing likelihood of completion or trial:

- (*a*) malignant disease;
- (*b*) residual papalysis due to cerebral damage with or without hypertension;
- (*c*) chronic advanced renal disease with systemic manifestations; or
- (*d*) cirrhosis of liver with systemic manifestations.

Annex 2

CRITERIA FOR REMOVAL FROM THE TRIAL ON MEDICAL GROUNDS

(1) Myocardial infarction—see " Definitions of endpoints " in text;

(2) hypertension—as for the criteria for rejection;

(3) other heart disease—which has previously not been recognized—as defined under rejection criteria 5, 6, and 7;

(4) diabetes mellitus—requiring drug treatment; or

(5) contraindications for taking capsules:

- (*a*) side effects that cannot be tolerated by the individual;
- (*b*) infective hepatitis and cirrhosis;
- (*c*) advanced renal disease; or
- (*d*) agranulocytosis or thrombocytopenic purpura.

Annex 3

COLLABORATING ORGANIZATIONS

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